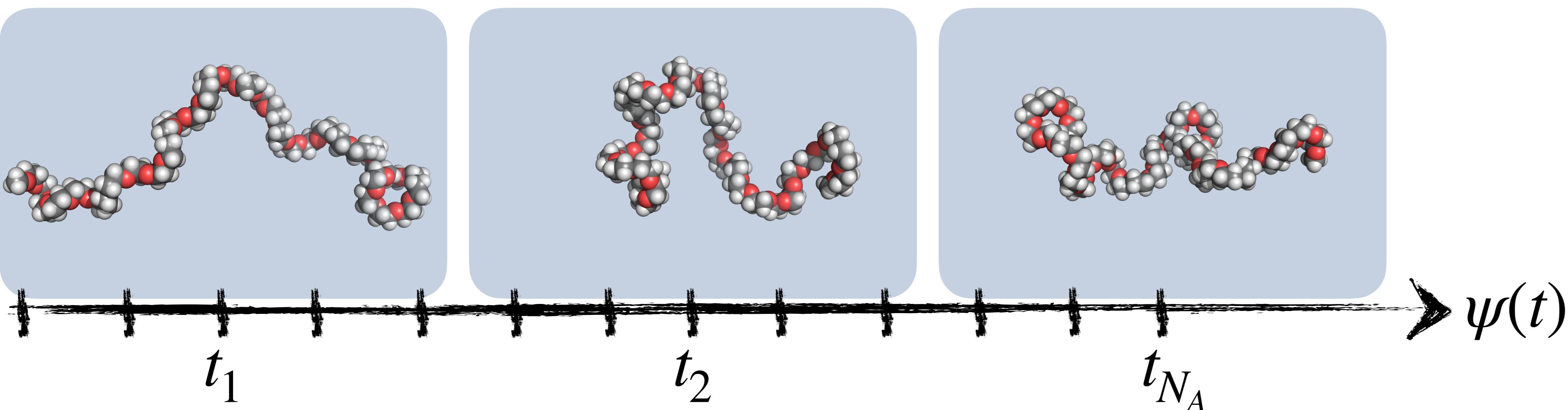
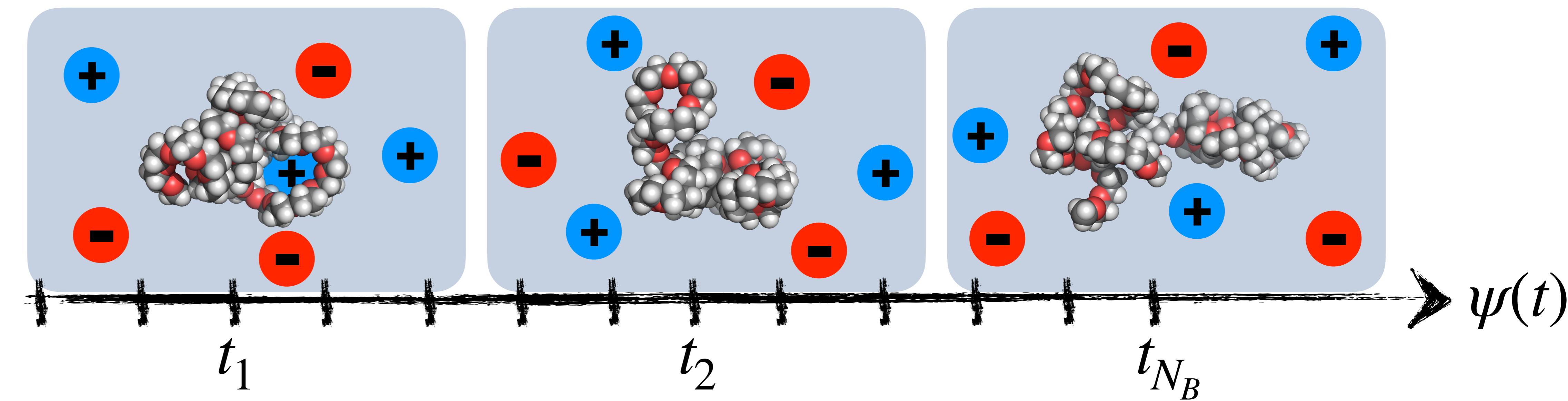


Step 1: Generation of ensembles of solute structures ψ

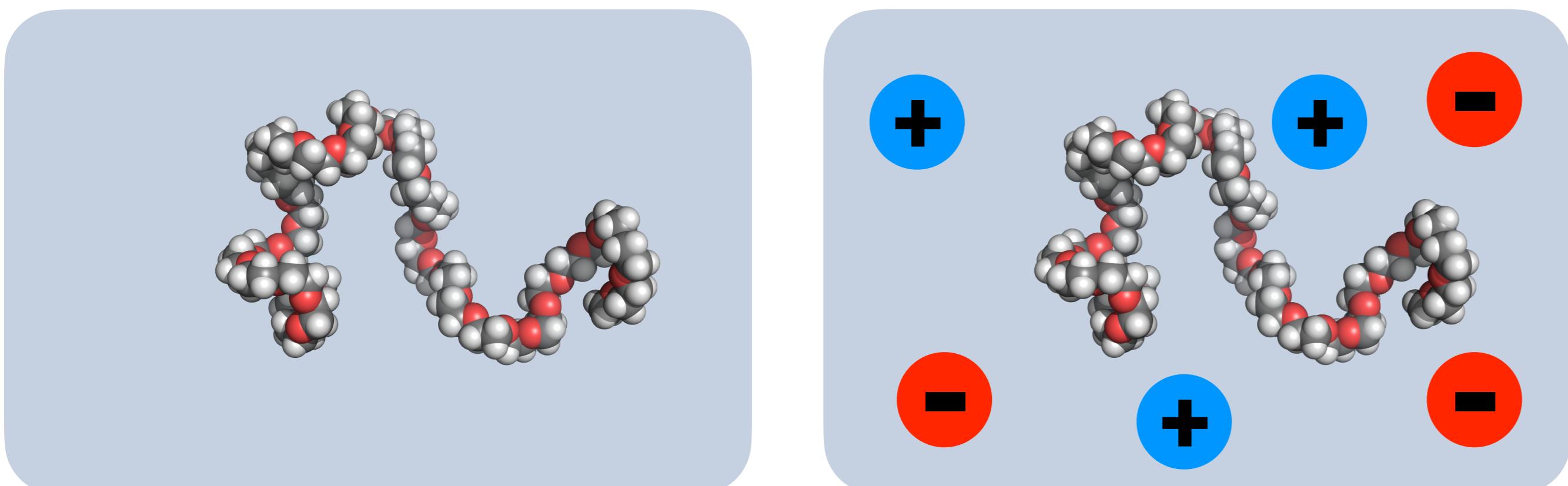
with $P_A(\psi)$



with $P_B(\psi)$



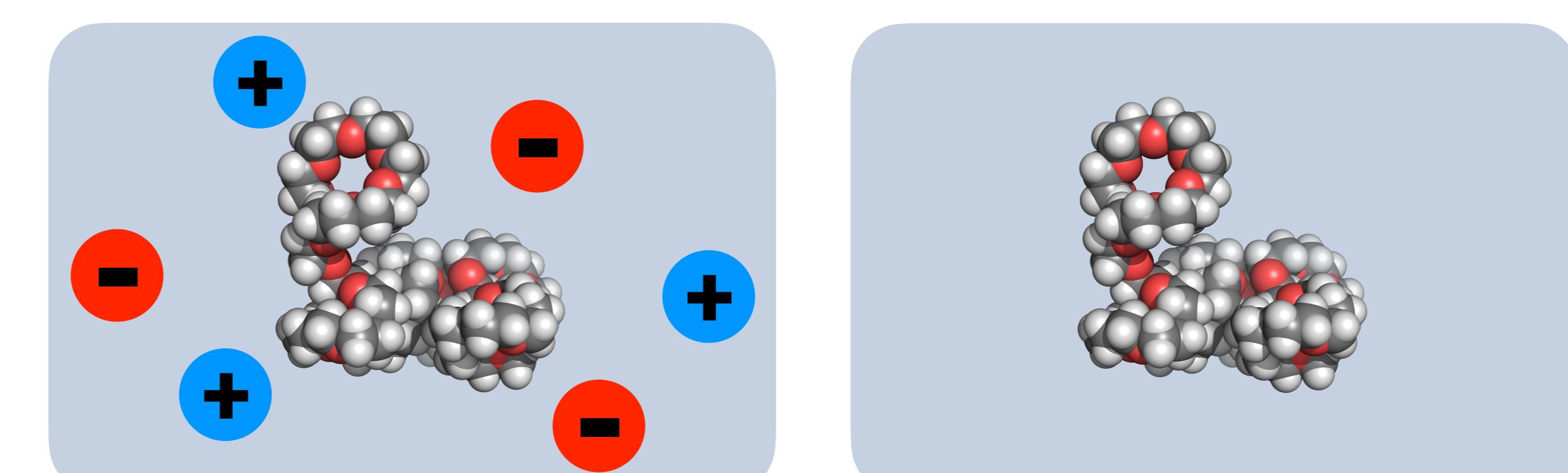
Step 2: Generation of solvent configurations in the presence of rigid solute and calculations of the solvation free energies



$$\nu_A^{\text{solv}}(\psi)$$

$$\nu_B^{\text{solv}}(\psi)$$

$$\Delta\nu^{\text{solv}}(\psi) = \nu_B^{\text{solv}}(\psi) - \nu_A^{\text{solv}}(\psi)$$



$$\nu_B^{\text{solv}}(\psi)$$

$$\nu_A^{\text{solv}}(\psi)$$

$$\Delta\nu^{\text{solv}}(\psi) = \nu_B^{\text{solv}}(\psi) - \nu_A^{\text{solv}}(\psi)$$

Step 3: Calculations of $\Delta\mu^{\text{ex}}$ and its upper and lower bounds

$$\sum_{\psi_i \in A, i=1}^{N_A} F \left(\Delta\nu^{\text{solv}}(\psi_i) - \Delta\mu^{\text{ex}} \right) = \sum_{\psi_i \in B, i=1}^{N_B} F \left(-\Delta\nu^{\text{solv}}(\psi_i) + \Delta\mu^{\text{ex}} \right)$$

$$\Delta\mu_{\text{upper}}^{\text{ex}} = \frac{1}{N_A} \sum_{\psi_i \in A, i=1}^{N_A} \Delta\nu^{\text{solv}}(\psi_i)$$

(equation for $N_A = N_B$)

$$\Delta\mu_{\text{lower}}^{\text{ex}} = \frac{1}{N_B} \sum_{\psi_i \in B, i=1}^{N_B} \Delta\nu^{\text{solv}}(\psi_i)$$